UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/333,110	06/15/99	STRAUS D	50050/002001

HM12/0217

PAUL T CLARK
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON MA 02110

EXAMINER	
EINSMANN, J	
ART UNIT	**PAPER NUMBER**
1655	3

DATE MAILED: 02/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/333,110	STRAUS, DON	
	Examiner	Art Unit	
	Juliet C. Einsmann	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *6/15/99; 11/3/99* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *21-46 and 55-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 47-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-20 and 47-54, drawn to methods for obtaining genetic information, classified in class 435, subclass 6.

II. Claims 21-46 and 55-57, drawn to oligonucleotide probes and kits, classified in class 536, subclass 24.3.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions II and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the probes and kits of group II can be used in materially different processes such as simple hybridization assays or peptide synthesis.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions I-II require different searches that are not coextensive, examination of these claims would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Paul Clark on 10/21/99 a provisional election was made without traverse to prosecute the invention I, claims 1-20 and 47-54. Affirmation of this

election must be made by applicant in replying to this Office action. Claims 21-46 and 55-57 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification- Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821-1.825 because there is no sequence listing and no CRF has been submitted. See, for example, pages 73 and 78. Applicant is required to submit a CRF and paper copy of the Sequence Listing containing these sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-20 and 47-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-20 and 48-54 are indefinite for failing to recite a final process step which agrees back with the preamble. Claims 1-20 and 48-54 are drawn to a method for obtaining genetic information, yet the claims recite a final step of contacting or comparing nucleic acid molecules

with a detection ensemble. The claims do not set forth the relationship between the contacting or comparing nucleic acid molecules with a detection ensemble and obtaining genetic information and therefore, it is not clear whether the claims are intended to be drawn to a method for obtaining genetic information or a method for contacting or comparing nucleic acid molecules with a detection ensemble. It is unclear from the method steps how the contacting or comparing step leads to obtaining genetic information. Claim 47 is indefinite because it is unclear how the final process step of identification of nucleic acid molecules relates to the preamble of obtaining genetic information.

Claims 1-20 and 48-54 are indefinite because it is unclear what comprises a detection ensemble. For example, it is unclear if the detection ensemble is meant to comprise only nucleic acids or could comprise other types of molecules such as proteins.

Claims 1-20 and 48-54 are indefinite over the recitation of "detecting target nucleic acid molecules" because it is unclear if one is to detect the target nucleic acid molecules of step a)(i) or those recited in the preamble of the claims. If the intention of the claim is to detect the target nucleic acid molecules of step a)(i), then it is unclear what is meant to be detected if one provided probes (as in step a)(ii)), amplification products (as in step a)(iii)) or genomic representations (as in step a)(iv)) instead of target nucleic acid molecules.

Claims 1-20 and 48-54 are indefinite because it is unclear how providing target nucleic acid molecules in step a)(i) and then detecting target nucleic acid molecules in step b) would result in obtaining any genetic information from the sample since what was provided would then have been detected.

Claim 4 is indefinite over the recitation of "are not immobilized as size fractionated fragments in a matrix" because it is unclear if the claim is meant to provide a limitation wherein the nucleic acid molecules are not immobilized at all or wherein the nucleic acid molecules could be immobilized but not as size fractionated fragments.

Claims 5 and 6 are indefinite because it is not clear how they are further limiting from the base claim. It is unclear whether the recited amplification sequences are meant to provide the amplification products of (iii) or if they are intended to amplify any nucleic acid in the sample. Further, it is unclear if the amplification sequences are to be added to the solution or if they are already present in the sample.

Claim 7 is indefinite over the recitation of "said method is used" because it is unclear if this is meant to be a further step in the recited method or if all of the previously recited steps are meant to be performed *in situ*.

Claim 11 is indefinite because the phrase "in the liquid phase" lacks proper antecedent basis because the claim does not previously recite a liquid phase.

Claim 15 is indefinite because it is not clear if the claim means that the two different nucleic acid molecules should be two different regions of the genome of each of the ten viruses or two different alleles of the each of the ten viruses.

Claims 16-19 are indefinite because over the recitation of "said genetic information is the identification of nucleic acids" because it is unclear how genetic information relates to identification. That is, the claim recites that "information is the identification" when in fact the information would be obtained by identification of the nucleic acid molecules. Amendment of

the claim to read "wherein said genetic information is the identity of nucleic acid molecules" would obviate this rejection.

Claims 16-19 are indefinite over the recitation of "6 or more of ..." because it is unclear, for example, if the claim is intended to require the identification of 6 or more *E. coli* or if the claim is intended to require the identification of 6 or more different nucleic acid molecules wherein the six or more are selected from the group consisting of those listed in the claim. Furthermore, it is unclear if the identification step is meant to require that all six of the nucleic acid molecules be present in the sample or if the assay is meant determine whether or not each individual pathogen is present in the sample.

Claims 52-53 are indefinite for the recitation of "the amplification products of step (a)(iv)" because step (a)(iv) refers to genomic representations, while step (a)(iii) refers to amplification products.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. Claims 1-6, 8-14, 20, and 47-52 are rejected under 35 U.S.C. 102(e) as being anticipated by Shuber (US PAT 5834181).

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14). Shuber teaches multiple embodiments for his invention.

With respect to claims 4 and 11, Shuber teaches that it may be desirable to hybridize the polymers to the target in solution, i.e. without having bound the target to a support (Col. 6, line 66-Col. 7, line 4).

With respect to claims 5 and 6, example 2 shows that to test for mutations which might cause the disease β-Thalassima (BT), one could use a single set of PCR primers to amplify target nucleic acids and then use14 different ASO probes in the detection step for identifying which mutations are present (See Col. 15, Table 1).

With respect to claims 8 and 14, Shuber further teaches that hybridized probes can be identified by the use of hybridization arrays, wherein members of the probe pool are separated from the target nucleic acids and re-hybridized to immobilized probes on an array (Col. 9, line 65-Col. 10, line 10). In this case, the method of Shuber comprises obtaining genetic information from a sample by (a) providing probes that hybridized to target nucleic acid molecules in a sample and (b) detecting the probes using an ensemble of probes, wherein the detection

ensemble is immobilized on an array, wherein the probes of step (a) were obtained by first hybridizing a probe pool (ensemble of ID probes) with the sample and then separating them from the sample.

With respect to claim 10, Shuber teaches an embodiment in which the target nucleic acid is bound to a solid phase matrix (Col. 6, line 42-43).

With respect to claim 12, Shuber teaches that oligonucleotide probes can be synthesized to contain sequences complementary to the target region and additional pre-determined sequences that act as "tags" (Col. 10, lines 25-27).

With respect to claims 9 and 13 and 52, Shuber discloses in example 9 embodiment of the invention in which ligation based techniques are used (Col. 25, heading Example 9). In this case, probes that are intended to hybridize with the target are ligation probes and the ligation probes flank the site of a genetic alteration (Col. 26, lines 14-16). Shuber teaches that some probes which identify gentetic alteration include ASO probes, which target small chages relative to the prevalent "wild type" sequence, including a single nucleotide (as in single nucleotide polymorphisms (SNP)) (Col. 4, lines 40-48). Shuber teaches that after ligation the ligated products can be amplified using LCR or PCR (Col. 26, lines 31-34), specifically teaching that one method for identification of ligated probes is to use the ligation product as a template for a linear amplification using a universal priming sequence (Col. 26, lines 63-66).

With respect to claims 50-51 in which greater than 20 or 50 probes must be used, note, as mentioned above, that Shuber teaches the methods of this invention can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14).

10. Claims 1-6, 8-9, 11-15, 19-20, 47-48 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Barany et al. (WO 97/31256).

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). The method comprises (a) providing a sample containing target nucleic acid molecules (p. 6, lines 13-15) (b) detecting the target nucleic acid molecules by means of a hybridization phase in which two probes suitable for ligation when hybridized adjacent to one another on a target nucleic acid are hybridized to a target molecule and ligated (p. 6, lines 25-30) and (c) identifying the nucleic acid molecule by means of a capture phase in which the probes are captured on an addressable array (p. 6, lines 35-40) and identity is determined based on their position on the array (p. 7, lines 3-7).

The method is exemplified in figure 8 wherein a single pair of amplification primers is used to amplify the region containing a mutation, and then a probe sets are used to detect different mutations in two different codons. In this example there are twenty possible mutation combinations. Barany et al. teach that the probe ligation reactions are solution based (p. 48, lines 30-31), and one of each set of probes to be ligated comprises an oligonucleotide tag that will be useful for capture on the addressable array (p. 6, line 30). Barany et al. teach that this method is useful to determine the presence of viruses in a sample, including HIV, human T-cell lymphocytotrophic virus, hepatitis viruses, Epstein-Barr Virus, cytomegalovirus, human papillomaviruses, orthomyxo viruses, paramyxo viruses, adenoviruses, corona viruses, bunya viruses, and toga viruses (p. 21, lines 11-16).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Bleiweiss et al. (J. of Reproductive Medicine, (Feb. 1992) 37(2) 151-156) or over Barany in view of Bleiweiss et al.

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14).

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). The method comprises (a) providing a sample containing target nucleic acid molecules (p. 6, lines 13-15) (b) detecting the target nucleic acid molecules by means of a hybridization phase in which two probes suitable for ligation when hybridized adjacent to one another on a target nucleic acid are hybridized to a target molecule and ligated (p. 6, lines 25-30) and (c) identifying the nucleic acid molecule by means of a capture phase in which the probes are captured on an addressable array (p. 6, lines 35-40) and identity is determined based on their

position on the array (p. 7, lines 3-7). The method is exemplified in figure 8 wherein a single pair of amplification primers is used to amplify the region containing a mutation, and then a probe sets are used to detect different mutations in two different codons. In this example there are twenty possible mutation combinations.

Neither Shuber nor Barany et al. teach the use of their method with in situ hybridization.

Bleiweiss et al. teach a method in which they identify human papillomavirus subtypes using in situ hybridization probes specific to recognize subtypes 6/11, 16/18, or 31/35/51 (p. 151-152).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an in situ hybridization as taught by Bleiweiss et al. in method of Shuber or in the method of Barany et al. because Bleiweiss teaches that in situ hybridization has the advantage of extreme sensitivity, and is preferable over Southern blot assays because of "its preservation of cellular and nuclear morphology, allowing precise localization of a positive signal (p. 154)."

13. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Barany et al.

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-

200 probes, preferably allele specific oligonucleotides (Col. 7, lines 11-14). Shuber teaches multiple embodiments for his invention.

In one embodiment, Shuber teaches that the nucleic acid to be identified comprise bacteria and their phages, viruses, fungi and protozoa (Col. 6, lines 5-9). Shuber teaches that the sample of nucleic acid can be isolated from a patient, particularly from any cell source or body fluid including blood cells, buccal cells, or tissue exudates at the site of infection (Col. 6, lines 13-23).

Shuber does not specifically identify any specific bacteria and their phages, viruses, fungi or protozoa that could be tested for in a nucleic acid sample.

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). Barany et al. teach that this method can be used to test for infectious diseases, including *Escherichia coli, Salmonella, Shigella, Pseudomonas, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Yersinia, Staphylococcus aureus, Streptococcus pneumonia, Corynebacteria, Legionella, Mycoplasma, Chlamydia, Enterococcus faecalis, Cryptococcus neoformans, Blastomyces detmatitidis, Histoplasma capsulatum, Coccidioides immitis, Candida albicans, Entamoeba, and Necator americanis* (p. 20, line 33- p. 21, line 23).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have tested for the nucleic acids of the specific pathogens taught by Barany et al. in the method taught by Shuber since Shuber teaches that his method can be used

for the identification specific nucleic acid sequences of "part of a foreign genetic sequence, e.g. the genome of an invading microrganism" including bacteria and their phages, viruses, fungi and protozoa (Col. 6, line6-7), and Barany et al. specifically list these bacteria and their phages, viruses, fungi and protozoa as pathogens that could be detected in a nucleic acid assay.

14. Claims 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Jarnik et al. or as being unpatentable over Barany et al. in view of Jarnik et al.

Shuber teaches methods for obtaining genetic information from a biological sample comprising (a) providing a sample containing target nucleic acid molecules and (b) detecting the target molecules by contacting the sample with hybridization probes and identifying the hybridized probes (abstract). Shuber specifically teaches that the method can be used with 10-200 probes, preferably allele specific oligonuclcotides (Col. 7, lines 11-14). Shuber discloses in example 9 embodiment of the invention in which ligation based techniques are used (Col. 25, heading Example 9). In this case, probes that are intended to hybridize with the target are ligation probes and the ligation probes flank the site of a genetic alteration (Col. 26, lines 14-16). Shuber teaches that some probes which identify gentetic alteration include ASO probes, which target small chages relative to the prevalent "wild type" sequence, including a single nucleotide (as in single nucleotide polymorphisms (SNP)) (Col. 4, lines 40-48). Shuber teaches that after ligation the ligated products can be amplified using LCR or PCR (Col. 26, lines 31-34), specifically teaching that one method for identification of ligated probes is to use the ligation product as a template for a linear amplification using a universal priming sequence (Col. 26, lines 63-66).

Barany et al. teach a method for identifying a plurality of sequences differing by one or more single base changes, insertions, deletions or translocations in a plurality of target nucleotide sequences (abstract). The method comprises (a) providing a sample containing target nucleic acid molecules (p. 6, lines 13-15) (b) detecting the target nucleic acid molecules by means of a hybridization phase in which two probes suitable for ligation when hybridized adjacent to one another on a target nucleic acid are hybridized to a target molecule and ligated (p. 6, lines 25-30) and (c) identifying the nucleic acid molecule by means of a capture phase in which the probes are captured on an addressable array (p. 6, lines 35-40) and identity is determined based on their position on the array (p. 7, lines 3-7). The method is exemplified in figure 8 wherein a single pair of amplification primers is used to amplify the region containing a mutation, and then a probe sets are used to detect different mutations in two different codons. In this example there are twenty possible mutation combinations.

Neither Shuber nor Barany teach the use of this method wherein amplification sequences are used to direct the amplification of sequences lying between Alu repeats using Alu-specific primers.

Jarnik et al. teach a method which comprises using inter-Alu PCR and using the PCR products as probes (p. 389, Col. 1) for the detection of genomic rearrangements and/or deletions in cancer cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used inter-Alu PCR and Alu probes in the method of Shuber or in the method of Barany et al. in order to have produced a method useful for detecting genomic

rearrangements and/or deletions in cancer cells, or for other types of cancer detection methods since Jarnik et al. teach "In addition to the detection of LOH, inter-Alu PCR typing systems also detect genomic instabilities occurring in certain hereditary as well as in a fraction of sporadic cancer cells (p. 397)."

Conclusion

15. No claims are allowed.

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Straus et al. (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 1889-1893) teach the addition adapters onto the ends of oligonucleotides in order to provide a region wherein primers could hybridized in a PCR reaction. Straus et al. that this is useful to enable the amplificaiton small amounts of DNA to proceed with an experiment (p 1891).

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Einsmann
Examiner
Art Unit 1655

February 14, 2000